

Dietary fat and risk of breast cancer^{1,2}

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ABSTRACT The relationship between dietary fat and subsequent risk of breast cancer was studied in 3988 initially cancer-free Finnish women aged 20–69 y. During a follow-up period of 20 y, 54 breast-cancer cases were diagnosed. Risk of breast cancer was significantly inversely related to energy intake and nonsignificantly inversely related to absolute fat intake. A positive association between energy-adjusted total fat intake and occurrence of breast cancer was also observed. The relative risk in the highest tertile as compared with the lowest tertile was 1.7 (95% confidence limits 0.6–4.8). The corresponding relative risks were 1.4 (0.5–3.7) for saturated fatty acids, 2.7 (1.0–7.4) for monounsaturated fatty acids, 1.2 (0.6–2.8) for polyunsaturated fatty acids, and 2.2 (1.0–5.0) for cholesterol intake. Adjustment for different potential confounding factors did not alter the results. The present data suggest that breast cancer is associated inversely with energy intake and weakly positively with energy-adjusted fat intake. *Am J Clin Nutr* 1990;52:903–8.

KEY WORDS Breast, cohort, diet, energy, epidemiology, fat, fatty acids, neoplasms

Introduction

The relationship between breast cancer and dietary fat has been debated for several years. Evidence for a positive association between this cancer and the absolute level of dietary fat is available primarily from animal experiments (1–4) and ecologic studies (5–10). The former generally implicate both total fat and polyunsaturated fatty acid intake whereas the latter demonstrate stronger relationships for saturated fatty acid or animal fat consumption. A protective role for the $n-3$ ($\omega-3$) fatty acids specifically has also been demonstrated in rodents and hypothesized for humans (11). In contrast, with the exception of three studies (12–14), several recent epidemiologic case-control (15–20) and cohort (21, 22) studies suggest no association, or in some cases a possible inverse relation, between absolute fat intake and risk of breast cancer. Only three of the studies (19, 21, 22) estimated risk associated with relative fat intake, ie, fat calories or grams relative to total calories. Two of these studies suggested that women consuming more of their calories from fat were at decreased risk (21, 22) and one (19) demonstrated elevated risk of developing breast cancer among such women. Moreover, information concerning various specific fatty acids has not been evaluated with respect to breast-

cancer risk in humans in these or other studies. Therefore, although some data implicate higher intake of total fats or of polyunsaturated, monounsaturated, or saturated fatty acids in the etiology of breast cancer, the evidence is far from conclusive and lacks critical corroboration from analytic studies in humans.

Using recently available food composition data concerning specific fatty acids (L. Hyvönen, unpublished observations, 1988), we studied the relationship between prospectively collected dietary histories and the subsequent development of breast cancer in a cohort of Finnish women.

Subjects and methods

Study population and case ascertainment

Between 1966 and 1972, the Social Insurance Institution's Mobile Clinic Health Examination Survey carried out multiphasic screening examinations in 30 different regions of Finland (23). From rural, semiurban, and industrial communities throughout the country, 62 440 adults aged ≥ 15 y were asked to participate in the study and 82.5% did so. A survey of dietary intake was administered to a random subsample of 10 054 participants as part of the main study (24, 25). Of these, 3988 were women aged 20–69 y who were not previously diagnosed as having cancer. Information concerning subsequent cancer incidence, available through the nationwide Finnish Cancer Registry (26), was linked to the dietary data to study the association between the level and kind of dietary fats and incidence of breast cancer. During a 20-y follow-up period between 1967 and 1986, 54 breast-cancer cases were diagnosed, identified, and histologically confirmed by the Cancer Registry.

Study data

At the baseline examination, data concerning usual food consumption during the previous year was collected by use of

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TABLE 1

Age-adjusted mean level of potential confounding factors among women who developed breast cancer (cases) and those who did not (noncases)

Factor	Cases (n = 54)	Noncases (n = 3934)
Age (y)	47.2 ± 12.4*	41.1 ± 13.7
Body mass index (kg/m ²)	25.0 ± 4.8	25.5 ± 4.6
Stature (cm)	160.9 ± 6.3	159.2 ± 6.1
Current smoker (%)	18.6	17.8
Nulliparous (%)	36.4	24.4
Premenopausal (%)	66.7	70.0
Rural (%)	25.1	36.2

* $\bar{x} \pm SD$.

the dietary history method (24, 27). The reliability of this method for fat, energy, and cholesterol intake during an interval of ~6 mo varied between 0.46 and 0.53 (28). Dietary fat and fatty acid intakes were calculated by use of recently available Finnish food composition values analyzed by capillary gas chromatography (L Hyvönen, unpublished observations, 1988). The fatty-acid-composition data of meat products were modified by appropriate conversion factors for the higher fat content of meat in the late 1960s and the early 1970s. The calculations of energy, protein, carbohydrates, and other nutrients were based on the Finnish food composition tables (29). Only available carbohydrates were included in carbohydrate values.

A self-administered questionnaire checked at the baseline examination supplied information about residence, occupation, parity, and smoking. Subjects were classified according to smoking status as nonsmokers (those who had never smoked and exsmokers combined) and current smokers. Women aged ≥ 50 y were classified as postmenopausal for the purposes of multivariate adjustments. Body height and weight were measured at the baseline examination and the body mass index (wt/ht²) was calculated.

Statistical methods

The age-adjusted mean levels of several descriptive and potential confounding factors among cancer cases and noncases were estimated by use of the general-linear-model procedure (30). Cox's proportional-hazards model was used to estimate the association between the dietary factors and risk of breast cancer adjusting for age and other possible confounders (31). Relative risks were computed for tertiles of intake, with the lowest tertile used as a referent category. Statistical significance was tested with the likelihood-ratio test based on the Cox models. Adjustment for energy was accomplished by including energy as a continuous variable in the multivariate model along with fat, ie, the "model method." The residual method described by Willett and Stampfer (32) and the technique to divide fat intake by energy intake, ie, the "fat-density method," were also used.

Results

Age-adjusted mean levels of potential confounding factors at the baseline for women who developed breast cancer (cases) and those who did not (noncases) are presented in Table 1.

Women who subsequently developed breast cancer were older, thinner, taller, and more likely to be nulliparous and from an urban area. The proportion of current smokers was relatively low overall and only slightly higher among women who developed breast cancer. All of the factors, with the exception of parity, were significantly associated with total intake of fat. The age-adjusted partial correlation coefficients were, however, very low, varying from 0.02 to 0.09.

Age-adjusted mean daily intakes of energy and dietary fat among cases and noncases are presented in Table 2. The mean energy intake was somewhat lower among breast cancer cases compared with noncases. Similar results were observed in total, saturated, and monounsaturated fatty acid intake, whereas polyunsaturated fatty acid intake was approximately equivalent between cases and noncases, and cholesterol intake was higher in cases. After adjustment for energy intake, the case means were slightly higher than noncase means with respect to intake of total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, and cholesterol. Because the energy-adjusted intake of nearly all of the fatty acid types (including n-3 and n-6 fatty acids) was consistently higher in cases, further analyses were conducted for major categories of fatty acids based on the level of saturation.

There were nonsignificant inverse gradients between absolute energy intake, total fat, saturated fatty acid, and polyunsaturated fatty acid intake and subsequent occurrence of breast cancer (Table 3). After adjustment for total fat intake, there was a significant inverse gradient between energy intake and risk of breast cancer ($P = 0.03$), the relative risk of breast cancer being 0.36 in the highest tertile of energy intake in comparison with the lowest tertile. There appeared to be nonsignificant positive gradients between risk of breast cancer and energy-adjusted indices of the different types of fat (saturated, monoun-

TABLE 2

Mean daily intake of fat and fatty acids for breast-cancer cases and noncases adjusted for age and energy intake

	Age adjusted		Age and energy adjusted*	
	Cases	Noncases	Cases	Noncases
Energy (kcal)	2009	2141	—	—
Total fat (% energy)	38.1	36.8	—	—
Total fat (g)	85.9	88.2	91.6	88.1
Saturated fatty acids (g)	47.9	49.8	51.2	49.8
C ₄ -C ₁₁	6.0	6.3	6.4	6.3
C ₁₂ -C ₁₈	41.7	43.3	44.6	43.3
C ₂₀ -C ₂₆	0.2	0.2	0.2	0.2
Monounsaturated fatty acids (g)	27.7	28.2	29.5	28.1
Polyunsaturated fatty acids (g)	6.4	6.4	6.8	6.3
n-3	1.2	1.2	1.3	1.2
n-6	4.8	4.7	5.0	4.7
Ratio of polyunsaturated to saturated fatty acids (P:S)	0.150	0.138	0.148	0.138
Cholesterol (mg)	410	407	433	406

* Energy intake in a regression model as a continuous variable.

TABLE 3

Relative risk (95% confidence limits) of breast cancer according to tertiles of energy and fat intake

Nutrient and tertile	Age adjusted		Age and energy adjusted*	
	Relative risk	95% Confidence limits	Relative risk	95% Confidence limits
Energy (kcal)				
<1792	1.0			
1792-2334	0.87	0.47, 1.59		
≥2335	0.58	0.29, 1.18		
	<i>P</i> for trend = 0.15			
Total fat (g)				
<71.2	1.0		1.0	
71.2-97.2	0.72	0.37, 1.39	0.99	0.46, 2.13
≥97.3	0.85	0.45, 1.60	1.72	0.61, 4.82
	<i>P</i> for trend = 0.62		<i>P</i> for trend = 0.10	
Saturated fatty acids (g)				
<39.6	1.0		1.0	
39.6-55.3	0.82	0.43, 1.56	1.05	0.50, 2.20
≥55.4	0.79	0.41, 1.51	1.36	0.50, 3.73
	<i>P</i> for trend = 0.48		<i>P</i> for trend = 0.31	
Monounsaturated fatty acids (g)				
<22.7	1.0		1.0	
22.7-31.0	0.87	0.43, 1.69	1.34	0.63, 2.86
≥31.1	1.04	0.55, 1.98	2.70	0.99, 7.37
	<i>P</i> for trend = 0.79		<i>P</i> for trend = 0.05	
Polyunsaturated fatty acids (g)				
<4.6	1.0		1.0	
4.6-6.7	0.97	0.51, 1.82	1.20	0.60, 2.41
≥6.8	0.86	0.44, 1.68	1.23	0.55, 2.75
	<i>P</i> for trend = 0.79		<i>P</i> for trend = 0.28	
P/S				
<0.11	1.0		1.0	
0.11-0.13	1.36	0.69, 2.69	1.36	0.69, 2.68
≥0.14	1.56	0.81, 3.03	1.50	0.77, 2.93
	<i>P</i> for trend = 0.30		<i>P</i> for trend = 0.38	
Cholesterol (mg)				
<316	1.0		1.0	
316-449	1.11	0.58, 2.15	1.47	0.73, 2.97
≥450	1.22	0.63, 2.37	2.21	0.97, 5.02
	<i>P</i> for trend = 0.81		<i>P</i> for trend = 0.09	

* Cox's model (31).

saturated, polyunsaturated), the ratio of polyunsaturated to saturated fatty acids (P/S), and cholesterol. The relative risk between the highest and lowest tertile of total fat intake was 1.72 (95% confidence limits 0.61 and 4.82) and of monounsaturated fatty acid intake, 2.70 (95% confidence limits 0.99 and 7.37). Adjustment for various potential confounders (age, parity, menopausal status, BMI, stature, smoking, and region type) or for intake level of several vitamins (including vitamins A, C, D, and E and carotene) did not notably alter the findings. The results also persisted when the data were adjusted for energy intake through either the technique that uses regression residuals or by the fat-density method. The performance of the adjustments by modeling was, however, unreliable because of the high correlation, 0.88, between fat and energy intake.

The possible modifying effects of smoking, BMI, stature, region type, menopausal status, and parity on the relationship between fat intake and occurrence of breast cancer were also studied. No significant interactions were observed. To minimize the possibility that preclinical disease affected dietary in-

take, cancer cases diagnosed during the first 5 y of follow-up were excluded. The results were not notably altered: the relative risk of cancer in the highest tertile of energy intake was 0.61 (95% confidence limits 0.28 and 1.32) and of relative fat intake, 2.08 (95% confidence limits 0.67 and 6.45).

Study of the association between the main sources of energy and risk of breast cancer showed an inverse association not only for fat intake but also for protein and carbohydrate intake (Table 4). When all three components were included simultaneously in a life-table regression model, it appeared, however, that the inverse association was mainly due to carbohydrate intake. Also, the association between the intake of some food groups (eg, fats and oils, vegetables, fruits and berries, cereals, milk products, eggs, fish, meat and meat products) and risk of breast cancer was studied. Persons with a high milk intake and persons with a low intake of meat and meat products had a decreased risk of breast cancer. The age-adjusted relative risk of cancer between the highest and the lowest tertile of milk intake was 0.40 ($P = 0.02$) and of meat intake, 1.76 ($P = 0.12$).

TABLE 4
Relative risk (95% confidence limits) of breast cancer according to tertiles of different components of energy intake

Nutrient and tertile	Age adjusted		Simultaneous adjustment*	
	Relative risk	95% Confidence limits	Relative risk	95% Confidence limits
Fat (g)				
<71.2	1.0		1.0	
71.2-97.2	0.72	0.37, 1.39	0.84	0.41, 1.70
≥97.3	0.85	0.45, 1.60	1.12	0.48, 2.63
	<i>P</i> for trend = 0.62		<i>P</i> for trend = 0.74	
Protein (g)				
<66.9	1.0		1.0	
66.9-86.5	1.02	0.55, 1.89	1.19	0.60, 2.38
≥86.6	0.72	0.36, 1.44	1.06	0.39, 2.85
	<i>P</i> for trend = 0.43		<i>P</i> for trend = 0.51	
Carbohydrate (g)				
<208	1.0		1.0	
208-277	0.63	0.34, 1.18	0.58	0.30, 1.13
≥278	0.50	0.25, 1.00	0.40	0.16, 1.00
	<i>P</i> for trend = 0.05		<i>P</i> for trend = 0.04	

* Cox's model including fat, protein, carbohydrate, and age as independent variables (31).

Adjustment for energy strengthened the meat-breast cancer association.

Discussion

The present longitudinal study demonstrates a nonsignificant inverse association between absolute fat intake and occurrence of breast cancer and a nonsignificant positive relationship between relative fat intake and breast cancer. Most components of dietary fat appear to contribute to the observed positive association.

The findings are based on dietary histories collected up to 20 y before the diagnosis of cancer, thereby reducing the potential influence of disease on either actual or reported intake. The results did not notably change when the cancer cases occurring during the first years of follow-up were excluded and it was thus improbable that the observed association is due to preclinical cancer. Case ascertainment through the national cancer registry was virtually complete (33) and therefore unbiased with respect to dietary intake. Also, very recently available food composition data concerning fatty acids (L Hyvönen, unpublished observations, 1988) were used and offered an opportunity to evaluate more specific dietary fat components.

Two recent cohort studies conducted in the United States demonstrated nonsignificant inverse associations between fat intake (both relative and absolute) and breast-cancer risk (21, 22). A semiquantitative food frequency questionnaire was used in one of these investigations (21), whereas in the other, a 24-h-recall questionnaire was administered (22). In these studies the average estimated intake of energy and total fat was 15-30% and 21-32% lower, respectively, than in the present investigation. Although the differences may be real, it is more likely that they are due to known limitations of dietary questionnaires (34, 35). In contrast, on the basis of data reported in one of these studies (22), the proportion of energy derived from fat sources was similar to what we observed. Therefore, whereas

energy and absolute-fat intake appear higher in our study population, the proportion of energy from fat may be more similar. This raises the possibility previously put forward (3) that relative fat intake may become more important with respect to breast carcinogenesis only at higher levels of total fat consumption.

Differences in the types of fat consumed by these separate populations may also have contributed to the divergent results. In our cohort, ~30% of dietary fat was derived from milk and milk products, 21% from meat and its products, and 34% from butter, margarine, and oils (25). In contrast, in the United States (36) these values are 12%, 38%, and 40%, respectively, reflecting substantial differences. The present study, in agreement with some prior studies (37-40), suggests a positive association between meat intake and breast cancer whereas it shows an inverse relationship for intake of milk and milk products. Alternatively, there could exist differences in the prevalence of other breast-cancer risk factors (eg, body size or lifestyle-related factors), which may interact with dietary fat consumption. Similar comparisons of such data between studies would be useful and may help explain some of the divergent results.

The present study is limited primarily by the relatively small number of cancer cases that occurred. Consistency of the observed association across various subgroups within the cohort reduces the likelihood that our findings are due to chance, however. Although information for some important potential confounders (age at menarche and first childbirth, a maternal history of breast cancer, and a history of benign breast disease) were not available for adjustment, the effects of others such as parity, stature, obesity, and socioeconomic status were controlled and did not alter the results. Also, only weak associations between dietary fat intake and potential confounders and effect modifiers have been observed by others (21, 22), thus reducing the likelihood that residual confounding is responsible for the present observations.

Alternatively, the strong associations between fat and energy

intake may have affected the results of this study. To eliminate potential instability resulting from colinearity, we adjusted for energy intake using three different techniques. Although the results were similar regardless of the method used, possible confounding by energy still cannot be completely excluded. On the other hand, the strength of the associations between fat intake and risk of cancer may be underestimated in the present study because of measurement errors in the dietary questionnaire (41) and changes in the dietary habits in Finland during the 20-y follow-up (42).

We observed a weak positive association between cholesterol intake and risk of breast cancer. With one exception (20), significant association between cholesterol intake and risk of breast cancer has not been reported previously (12, 18, 19, 21, 22). Our result is, however, supported by a similar finding in some previous studies of serum cholesterol concentrations (43).

The ways in which increased dietary fat intake could theoretically enhance breast carcinogenesis have been outlined by several authors (44). Among the more prominent hypotheses are that fat could affect steroid hormones, prostaglandins, the immune system, cell membranes, or energy balance. That energy intake was lower among women who later developed breast cancer, a finding consistent with some (19, 22) but not all (12, 20, 21) previous studies, suggests alternative explanations as well. Cases may have experienced lower intake of foods rich in vitamins or minerals, some of which are believed to inhibit carcinogenesis (45). Adding the intake level of several vitamins (including vitamins A, C, D, and E) to the regression models changed the relative risk estimates only a little, however. Confounding by micronutrient consumption therefore does not explain our findings. Alternatively, reduced energy consumption may indicate lower levels of physical activity (32). Inactivity or reduced activity levels have been associated with increased breast-cancer risk, especially among postmenopausal women (46). Unfortunately, physical activity was not measured in the present study. Energy intake may also differ among populations and thus relationships between relative fat intake and risk of cancer may differ in different populations.

The finding that adjustment for fat intake strengthened the inverse association between energy intake and risk of breast cancer suggests that the apparent protective effect of high energy intake is not due to fat intake. We, therefore, also studied the relation between breast cancer and the two other components of metabolizable energy, protein and carbohydrate intake. We found a significant inverse association with respect to carbohydrate intake. This finding is supported by a previous study that showed nonsignificantly lower levels of carbohydrate intake among breast-cancer cases compared with controls (19). In agreement with some studies (16, 18–20), protein intake was not related to risk of breast cancer in the present study. Others have suggested a positive association (13, 14, 37, 40).

In summary, we demonstrated an inverse relationship between energy and carbohydrate intake and occurrence of breast cancer. A weak inverse association between absolute fat intake and risk of breast cancer was also observed. In contrast, women with high relative fat intake had marginally elevated risk of breast cancer. Because of the high correlation between fat and energy intake, and the small number of cases involved, no strong conclusions regarding dietary fat intake and the risk of

breast cancer can be drawn from the present data. The issue should be further investigated in longitudinal studies of large cohorts, which would permit evaluation of the fat-breast cancer association at different levels of energy intake.

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